Refine Search

Search Results -

Terms	Documents
200269900	1

Database:
US Pre-Grant Publication Full-Text Database
US Patents Full-Text Database
US OCR Full-Text Database
EPO Abstracts Database
JPO Abstracts Database
Derwent World Patents Index
IBM Technical Disclosure Bulletins

Search: L4

Refine Search

Recall Text | Clear | Interrupt

Search History

DATE: Monday, June 18, 2007 **Purge Queries** Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=EPAB,JPAB,DWPI; PLUR=YES; OP=OR			
L4	200269900	1	L4
L3	2002699900	0	L3
L2	2253211	7	L2
DB=USPT; PLUR=YES; OP=OR			
L1	5961978.pn.	1	L1

END OF SEARCH HISTORY

Gleevec therapy in myelofibrosis with myeloid metaplasia (MMM)

AUTHOR: Tefferi Ayalew (Reprint); Mesa Ruben A (Reprint); Gray Leigh A (Reprint); Steensma David P (Reprint); Camoriano John K; Elliott Michelle A (Reprint); Pardanani Animesh (Reprint); Ansell Stephen M (Reprint); Call Timothy G (Reprint); Colon-Otero Gerardo; Geyer Susan M (Reprint); Hanson Curtis A (Reprint); Dewald Gordon W (Reprint); Kaufmann Scott H (Reprint)
AUTHOR ADDRESS: Mayo Clinic Rochester, Rochester, MN, USA**USA
JOURNAL: Blood 98 (11 Part 1): p626a November 16, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001; 20011207
SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: Gleevec (STI571) is an orally bioavailable 2-phenylaminopyrimidine derivative that stabilizes an inactive conformation of several transforming kinases, including bcr/***abl*** , the platelet derived growth factor (PDGF) receptor and c-Kit. This agent has demonstrated impressive hematological as well as cytogenetic response rates in chronic phase chronic myeloid leukemia (CML) as well as anti-tumor activity in Kit-dependent gastrointestinal stromal tumors. Because PDGF has been implicated in the pathogenesis of MMM, we evaluated the efficacy of Gleevec in this disorder. Patients: Between May and June of 2001, twenty patients (median age, 64.5 years; 17 males) with MMM were enrolled in a phase II treatment protocol using Gleevec at a constant dose of 400 mg/day. Before treatment with Gleevec, 8 patients were red blood cell (RBC) transfusion-dependent, 6 had a hemoglobin level above 10 g/dL, 6 were previously treated with chemotherapy, and 7 were in a high-risk prognostic category (Dupriez B. et al. Blood 88:1013, 1996). None of the patients were splenectomized and the median palpable spleen size was 10 cm below the left costal margin. Results: After a median follow-up duration of 2.5 months, treatment at 400 mg/day was held in 11 (55%) of the 20 patients because of side effects. These included moderate (absolute neutrophil count (ANC)<1X109/L) to severe (ANC<0.5X109/L) neutropenia (5 cases), peripheral edema (2 cases), musculoskeletal/limb pain (2 cases), extreme thrombocytosis (1 case), and diarrhea (1 case). Re-treatment at a reduced dose of 200 mg/day was possible in only 3 of the 11 patients because of either persistence or recurrence of toxicity. In addition, severe reversible hyperbilirubinemia (bilirubin, 10.9 mg/dL) was seen in one patient. Overall, 25% of patients were removed from therapy because of adverse effects. Drug-associated neutropenia occurred in 6 of 10 (60%) patients with a pre-treatment white blood cell count (WBC) of <5X109/L but in 0 of 10 patients with a baseline WBC>5X109/L. Similarly, both fluid retention and musculoskeletal pain occurred in only those patients with a previous history of the same. To date, none of the patients experienced favorable changes in RBC transfusion dependency, hemoglobin level, or spleen size. A >50% increase in platelet count was documented in 11 patients (55%) including two cases where the platelet count exceeded 1000X109/L. However, increased platelet counts were often transient and failed to occur in the two patients with baseline platelet counts of <100X109/L. Effects of Gleevec on growth of peripheral blood myeloid or erythroid colony forming cells ex vivo did not correlate with the in vivo drug effect on either platelet or neutrophil count. Conclusion: Borderline or overt leukopenia is a risk factor for severe drug-induced neutropenia during treatment of MMM with Gleevec. Similarly, the drug may exacerbate both edema and musculoskeletal symptoms in MMM. The high prevalence of drug-associated increase in platelet count is biologically interesting but may not be clinically useful. The current results are preliminary and the effects from a longer treatment duration

as well as a higher drug dose are being investigated.

2001

ABSTRACT: Background: Gleevec (STI571) is an orally bioavailable 2-phenylaminopyrimidine derivative that stabilizes an inactive conformation of several transforming kinases, including bcr/***abl*** , the platelet derived growth factor (PDGF) receptor and c-Kit. This agent has demonstrated impressive...
?

Identification of Small Molecule Inhibitors of BCR/ABL Tyrosine Kinase through Structure Based Virtual Screening.
AUTHOR: Peng Hui (Reprint); Qi Jing (Reprint); Huang Niu (Reprint); Yang Chunzheng (Reprint); Wang Jiangxiang (Reprint)
AUTHOR ADDRESS: State Key Laboratory of Experimental Hematology, Institute of Hematology, CAMSandPUMC, Tianjin, China**China
JOURNAL: Blood 100 (11): pAbstract No. 1234 November 16, 2002 ***2002***
MEDIUM: print
CONFERENCE/MEETING: 44th Annual Meeting of the American Society of Hematology Philadelphia, PA, USA December 06-10, 2002; 20021206
SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Poster; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Over 90% of chronic myelogenous leukemia (CML) and 10% to 25% of adult acute lymphoblastic leukemia (ALL) are associated with a reciprocal translocation between chromosomes 9 and 22 that produces a Bcr-Abl fusion gene. Since transformation by BCR/ABL is absolutely dependent on tyrosine kinase activity, it has been evident that BCR/ABL tyrosine kinase domain could be an attractive target for drug development. Herein, we describe the discovery of novel classes of small molecule inhibitors targeted at the catalytic domains of Abl tyrosine kinase, in which a centrally located "activation loop" is not phosphorylated, by computational 3-D database search. A preliminary DOCK screening against the distinctive inactive conformation of the catalytic domain of BCR/ABL was performed on a smaller 3D database that 202,657 commercially available organic compounds had been built via in-house procedures. 20,000 top compounds with steric complementarity to the binding site was selected for rigorous secondary DOCK screening. The docked complex geometries was used for rescoring by other representively scoring functions. 1000 compounds with a high potential to have high scores by different scoring functions was selected for further diversity analysis. From different structurally diverse clusters, 15 compounds were selected for biological assay based on physico-chemical properties, chemical stability, potential toxicity and potential metabolism. Nine of the 15 showed inhibitory activity against Ph+ human K562 cells with IC50 value ranging from 0.4 to 100 mug/ml. Analysis of the computer-generated binding modes showed that the active compounds interacted nicely with inactive conformation of the activation loop in the down-regulated form of ABL tyrosine kinase. The structural details and the unique binding motif may contribute to the future development of BCR/ABL tyrosine kinase inhibitors.

2002

...ABSTRACT: phosphorylated, by computational 3-D database search. A preliminary DOCK screening against the distinctive inactive conformation of the catalytic domain of BCR/ABL was performed on a smaller 3D database that 202,657 commercially available organic compounds had...

3/3,K,AB/7 (Item 3 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

16626728 BIOSIS NO.: 200200220239
Gleevec therapy in myelofibrosis with myeloid metaplasia (MMM)
AUTHOR: Tefferi Ayalew (Reprint); Mesa Ruben A (Reprint); Gray Leigh A (Reprint); Steensma David P (Reprint); Camoriano John K; Elliott Michelle A (Reprint); Pardanani Animesh (Reprint); Ansell Stephen M (Reprint);

Call Timothy G (Reprint); Colon-Otero Gerardo; Geyer Susan M (Reprint); Hanson Curtis A (Reprint); Dewald Gordon W (Reprint); Kaufmann Scott H (Reprint)
AUTHOR ADDRESS: Mayo Clinic Rochester, Rochester, MN, USA**USA
JOURNAL: Blood 98 (11 Part 1): p626a November 16, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001; 20011207
SPONSOR: American Society of Hematology
ISSN: 0006-4971

Multiple BCR-ABL kinase domain mutations confer polyclonal resistance to the tyrosine kinase inhibitor imatinib (STI571) in chronic phase and blast crisis chronic myeloid leukemia.

Shah Neil P; Nicoll John M; Nagar Bhushan; Gorre Mercedes E; Paquette Ronald L; Kuriyan John; Sawyers Charles L

Department of Medicine, Jonsson Comprehensive Cancer Center, David Geffen School of Medicine, University of California, Los Angeles, CA 90095, USA.

Cancer cell (United States) Aug 2002, 2 (2) p117-25, ISSN 1535-6108--Print Journal Code: 101130617

Contract/Grant No.: GM07185; GM; NIGMS

Publishing Model Print; Comment on Cancer Cell. 2002 Aug;2(2) 99-102; Comment on PMID 12204529

Document type: Comment; Journal Article; Research Support, Non-U.S. Gov't ; Research Support, U.S. Gov't, P.H.S.

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

(103)

Through sequencing analysis of blood or bone marrow samples from patients with chronic myeloid leukemia, we identified BCR-ABL kinase domain mutations in 29 of 32 patients whose disease relapsed after an initial response to the tyrosine kinase inhibitor imatinib. Fifteen different amino acid substitutions affecting 13 residues in the kinase domain were found. Mutations fell into two groups-those that alter amino acids that directly contact imatinib and those postulated to prevent BCR-ABL from achieving the inactive conformational state required for imatinib binding. Distinct mutations conferred varying degrees of imatinib resistance. Mutations detected in a subset of patients with stable chronic phase disease correlated with subsequent disease progression. Multiple independent mutant clones were detected in a subset of relapsed cases. Our data support a clonal selection model of preexisting BCR-ABL mutations that confer imatinib resistance.

```
 File 155:MEDLINE(R) 1950-2007/Jun 13
        (c) format only 2007 Dialog
*File 155: Medline has been reloaded. Please see HELP NEWS 154
for information on 2007 changes.
  File  55:Biosis Previews(R) 1993-2007/Jun W2
        (c) 2007 The Thomson Corporation
  File  34:SciSearch(R) Cited Ref Sci 1990-2007/Jun W3
        (c) 2007 The Thomson Corp
  File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec
        (c) 2006 The Thomson Corp

      Set  Items  Description
      ---  -----  -----------
? s (Bcr(w)ABL) (5n) conformation?
          27076  BCR
          26734  ABL
         533931  CONFORMATION?
      S1     42  (BCR(W)ABL) (5N) CONFORMATION?
? rd
      S2     25  RD  (unique items)
? s s2 and py<2004
Processing
             25  S2
       42962526  PY<2004
      S3      7  S2 AND PY<2004
? t s3/3,k,ab/1-7

 3/3,K,AB/1     (Item 1 from file: 155
```

SYSTEM:OS - DIALOG OneSearch
File 155:MEDLINE(R) 1950-2007/Jun 11
(c) format only 2007 Dialog
*File 155: Medline has been reloaded. Please see HELP NEWS 154 for information on 2007 changes.
File 55:Biosis Previews(R) 1993-2007/Jun W1
(c) 2007 The Thomson Corporation
File 34:SciSearch(R) Cited Ref Sci 1990-2007/Jun W2
(c) 2007 The Thomson Corp
File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec
(c) 2006 The Thomson Corp

```
      Set  Items  Description
      ---  -----  -----------
? s bcr(w)abl
           27048  BCR
           26705  ABL
      S1   17747  BCR(W)ABL
? s antibod?
      S2 1678559  ANTIBOD?
? s s1 and s2
           17747  S1
         1678559  S2
      S3     909  S1 AND S2
? s conformation?
      S4  533524  CONFORMATION?
? s s3 and s4
             909  S3
          533524  S4
      S5      10  S3 AND S4
? rd
      S6       8  RD  (unique items)
? t s6/3,k,ab/1-8
```

6/3,K,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12188825 PMID: 10602778
Circular antisense oligonucleotides inhibit growth of chronic myeloid leukemia cells.
Rowley P T; Kosciolek B A; Kool E T
Department of Medicine and Division of Genetics, University of Rochester, NY 14642, USA. peter rowley@urmc.rochester.edu
Molecular medicine (Cambridge, Mass.) (UNITED STATES) Oct 1999, 5 (10) p693-700, ISSN 1076-1551--Print Journal Code: 9501023
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
BACKGROUND: Antisense represents a conceptually powerful method for regulating gene expression. However, antisense oligonucleotides developed to date manifest two serious limitations-nuclease susceptibility and nonspecific hybridization. Circular oligonucleotides may be superior to conventional linear oligonucleotides in both respects. First, circular agents, having no ends, are exonuclease-resistant. Second, they bind to complementary strands of RNA and DNA with a higher affinity than corresponding linear agents. METHODS AND RESULTS: We assessed the activity of circular phosphodiester deoxynucleotides using chronic myeloid cell lines by targeting polypurine sequences. To represent cells having a bcr3/abl2-type junction, we used K562 cells. A circle targeting a bcr polypurine sequence 385 nucleotides 5' to the junction decreased the cell number by day 5 with an IC(50) of 9 microM. To represent cells having a

bcr2/abl2-type junction, we used BV173 cells. A circle targeting the bcr-abl junction itself decreased the cell number by day 7 with an IC(50) of 8 microM. Control oligonucleotides, whether the same sequence uncircularized or circles with the same nucleotide composition but in scrambled sequence, had little effect. Unlike linear agents, circles were stable when incubated in 10% serum. The amount of ***bcr*** - ***abl*** protein detected by Western blotting using a specific anti-bcr-abl antibody at 24 hr in antisense-treated BV173 cells was only 10% of that of cells treated with control circles, which demonstrates an antisense mechanism of action. CONCLUSIONS: Circular oligodeoxyribonucleotides (1) inhibit the accumulation of CML cells, (2) decrease the amount of bcr-abl protein per cell, (3) have sequence-selective activity, and (4) are more active than linear oligonucleotides containing only the base-pairing region.

... cells having a bcr2/abl2-type junction, we used BV173 cells. A circle targeting the bcr-abl junction itself decreased the cell number by day 7 with an IC(50) of 8...

... effect. Unlike linear agents, circles were stable when incubated in 10% serum. The amount of ***bcr*** - ***abl*** protein detected by Western blotting using a specific anti-bcr-abl antibody at 24 hr in antisense-treated BV173 cells was only 10% of that of cells...

... CONCLUSIONS: Circular oligodeoxyribonucleotides (1) inhibit the accumulation of CML cells, (2) decrease the amount of bcr-abl protein per cell, (3) have sequence-selective activity, and (4) are more active than linear...

; Base Sequence; Fusion Proteins, bcr-abl--genetics--GE; Humans; K562 Cells; Nucleic Acid Conformation; Oligonucleotides, Antisense--chemistry--CH

Chemical Name: Fusion Proteins, bcr-abl; Oligonucleotides, Antisense

6/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10490125 PMID: 7786800

Modulation of cell kinetics and cell cycle status by treating CD34+ chronic myeloid leukaemia cells with p53 antisense phosphorothioate oligonucleotides.

Lanza F; Bi S; Moretti S; Castoldi G; Goldman J M
Institute of Haematology, University of Ferrara, Italy.

British journal of haematology (ENGLAND) May 1995, 90 (1) p8-14, ISSN 0007-1048--Print Journal Code: 0372544
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Mutations of the p53 tumour suppressor gene occur in 20% of chronic myeloid leukaemia (CML) patients in blastic crisis, but it is still uncertain whether this inactivation plays a role in the pathogenesis of blastic transformation or in maintaining the leukaemic proliferation in CML, as it does in several solid tumours. We have previously shown that more than 50% of both normal and CML CD34+ cells express the p53 protein. However, haemopoietic cells at different phases of the cell cycle express p53 with different conformations, suggesting that the function of p53 may be closely regulated during the cell cycle. In order to elucidate the mechanism by which p53 suppresses cell proliferation, we evaluated the effects of inhibiting p53 expression on cell cycle and cell kinetics of chronic phase CML (n = 12) and normal (n = 7) bone marrow light-density

cells and purified CD34+ progenitors by using an 18-mer modified antisense oligonucleotide which targets the region covering the six base pairs immediately before the first codon and the first four coding codons of p53. We found that the number of cells positive for the cell cycle-specific nuclear antigen Ki67 and for the BrdU monoclonal antibody (McAb) was significantly increased after p53 antisense oligonucleotide treatment. At the same time, p53 protein expression was completely abrogated in both light-density and CD34+ cells. In addition, DNA analysis by flow cytometry demonstrated that the number of cells in quiescent phases of the cell cycle (G0-G1) was significantly decreased after exposure of light-density cells to p53 antisense oligomers, whereas the number of cells in S or G2-M phases was increased. Furthermore, the longer the incubation time the higher the increase in cell proliferation. Treatment of CML, cells with p53 antisense oligomers also resulted in significantly increased numbers of CFU-GM colonies. Our data suggest that p53 is a negative regulator of cell proliferation and its action is mediated through changes in cell cycle kinetics, mainly before the S phase. We can further speculate that the loss of p53 function, at the time of blastic crisis of CML, may play a role, in combination with other genetic changes (p210 BCR/ABL, Rb gene abnormality, others to be defined), in inducing disturbances in cell proliferation, differentiation, and apoptosis.

... protein. However, haemopoietic cells at different phases of the cell cycle express p53 with different conformations, suggesting that the function of p53 may be closely regulated during the cell cycle. In...

... cells positive for the cell cycle-specific nuclear antigen Ki67 and for the BrdU monoclonal antibody (McAb) was significantly increased after p53 antisense oligonucleotide treatment. At the same time, p53 protein...

... blastic crisis of CML, may play a role, in combination with other genetic changes (p210 BCR/ABL, Rb gene abnormality, others to be defined), in inducing disturbances in cell proliferation, differentiation, and...

6/3,K,AB/3 (Item 1 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

18787416 BIOSIS NO.: 200600132811
Treatment with the heat shock protein (hsp) 90 inhibitor17-dimethylaminoethylamino-17-demethoxygeldanamycin (DMAG) abrogates the levels and activity of the receptor tyrosine kinase TrkA in acute leukemia cells
AUTHOR: Kumaraswamy Sandhya (Reprint); Lambert Que T; Rocha Kathy; Bali Purva; Fiskus Warren; Balasis Maria; Pranpat Michael; Boyapalle Sandhya; Hannah Alison; Reuther Gary W; Bhalla Kapil
AUTHOR ADDRESS: Univ S Florida, Coll Med, H Lee Moffitt Canc Ctr and Res Inst, Tampa, FL 33612 USA**USA
JOURNAL: Blood 106 (11, Part 2): p179B NOV 16 2005 2005
CONFERENCE/MEETING: 47th Annual Meeting of the American-Society-of-Hematology Atlanta, GA, USA December 10 -13, 2005; 20051210
SPONSOR: Amer Soc Hematol
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Nerve growth factor (NGF) mediates the phosphorylation and signaling through the receptor tyrosine kinase TrkA, which has been shown to be expressed and active in the early hemopoietic progenitor cells, as well as in the K562 and TF1 leukemia cell lines and AML-ETO-expressing

human acute leukemia cells. In AML, a 75-amino acid deletion mutant of TrkA (Delta TrkA) has also been demonstrated to be constitutively active as a pro-growth and pro-survival protein through ERK1/2 and Akt activation. We have previously reported that that the ATP bound molecular chaperone hsp90 binds the leukemia associated Bcr-Abl and FLT-3 tyrosine kinases as client proteins, maintaining them in a property folded and active conformation, and that geldanamycin analogue hsp90 inhibitors disrupt this chaperone association, resulting in polyubiquitylation and proteasomal degradation of the client proteins. In the present studies, we investigated a) whether TrkA is a client protein of hsp90 and b) the effect of the novel and highly soluble hsp90 inhibitor DMAG (Kosan Biosciences Inc.) on TrkA levels and activity in mouse myeloid 32D cells with or without the ectopic expression of Delta TrkA (32D/Delta TrkA cells), as well as on endogenous levels of wild-type (WT) TrkA in K562 and TF1 cells. Exposure to 0.25 or 1.0 mu M DMAG attenuated the levels of WT TrkA in K562, TF1 and 32D, as well as Delta TrkA in 32D/Delta TrkA cells. Co-treatment with the proteasome inhibitor bortezomib (100 nM) restored DMAG mediated depletion of WT TrkA in K562 cells, suggesting that DMAG induced the polyubiquitylation and degradation of TrkA by the 26S proteasome. In K562 cells, immunoprecipitation (IP) with monoclonal anti-TrkA antibody followed by immunoblot (IB) analyses with anti-hsp90 antibody (or IP with anti-hsp90 followed by IB with anti-TrkA antibody) showed that TrkA binds to hsp90, which is inhibited by treatment with DMAG. Following suspension of K562 cells in a serum free medium containing 100 ng/ml of NGF, the levels of pTrkA, pERK1/2 and pAkt significantly increased within 5 to 10 minutes. Co-treatment with 1.0 mu M DMAG inhibited pTrkA arid pERK1/2 induction. suggesting that hsp90 chaperone function may be required for TrkA activity. Exposure to DMAG also depleted the levels of the other hsp90 client proteins, including c-Raf, Akt arid 13cr-Abl in K562 cells, which was associated with growth arrest and apoptosis in a dose-dependent manner. These findings demonstrate that TrkA may be an hsp90 client protein, and hsp90 inhibition by treatment with DMAG would deplete WT or mutant TrkA levels and activity in human leukemia cells. These findings suggest that hsp90 inhibitors may be effective against human acute leukemia cells that may depend on the activity of mutant or WT TrkA for growth and survival.

...ABSTRACT: have previously reported that that the ATP bound molecular chaperone hsp90 binds the leukemia associated Bcr-Abl and FLT-3 tyrosine kinases as client proteins, maintaining them in a property folded and active conformation, and that geldanamycin analogue hsp90 inhibitors disrupt this chaperone association, resulting in polyubiquitylation and proteasomal...

...of TrkA by the 26S proteasome. In K562 cells, immunoprecipitation (IP) with monoclonal anti-TrkA antibody followed by immunoblot (IB) analyses with anti-hsp90 antibody (or IP with anti-hsp90 followed by IB with anti-TrkA antibody) showed that TrkA binds to hsp90, which is inhibited by treatment with DMAG. Following suspension...

DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: Bcr-Abl;

6/3,K,AB/4 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

12885761 Genuine Article#: 828TX Number of References: 50
Title: The ErbB/HER receptor protein-tyrosine kinases and cancer (ABSTRACT AVAILABLE)
Author(s): Roskoski R (REPRINT)
Corporate Source: Louisiana State Univ,Hlth Sci Ctr, Dept Biochem & Mol

Biol,1100 Florida Ave/New Orleans//LA/70119 (REPRINT); Louisiana State Univ,Hlth Sci Ctr, Dept Biochem & Mol Biol,New Orleans//LA/70119(biocrr@lsuhsc.edu)
Journal: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, 2004, V319, N1 (JUN 18), P1-11
ISSN: 0006-291X Publication date: 20040618
Publisher: ACADEMIC PRESS INC ELSEVIER SCIENCE, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA
Language: English Document Type: EDITORIAL MATERIAL
Abstract: The ErbB/HER protein-tyro sine kinases, which include the epidermal growth factor receptor, consist of a growth-factor-binding ectodomain, a single transmembrane segment, an intracellular protein-tyrosine kinase catalytic domain, and a tyrosine-containing cytoplasmic tail. The genes for the four members of this family, ErbB1-ErbB4, are found on different human chromosomes. Null mutations of any of the ErbB family members result in embryonic lethality. ErbB1 and ErbB2 are overexpressed in a wide variety of tumors including breast, colorectal, ovarian, and non-small cell lung cancers. The structures of the ectodomains of the ErbB receptors in their active and inactive conformation have shed light on the mechanism of receptor activation. The extracellular component of the ErbB proteins consists of domains I-IV. The activating growth factor, which binds to domains I and 111, selects and stabilizes a conformation that allows a dimerization arm to extend from domain II to interact with an ErbB dimer partner. As a result of dimerization, protein kinase activation, trans-autophosphorylation, and initiation of signaling occur. The conversion of the inactive to active receptor involves a major rotation of the ectodomain. The ErbB receptors are targets for anticancer drugs. Two strategies for blocking the action of these proteins include antibodies directed against the ectodomain and drugs that inhibit protein-tyrosine kinase activity. A reversible ATP competitive inhibitor of ErbB1 (ZD1839, or Iressa) and an ErbB1 ectodomain directed antibody (IMC-C225, or Erbitux) have been approved for the treatment of non-small cell lung cancer and colorectal cancer, respectively. An ErbB2/HER2 ectodomain directed ***antibody*** (trastuzumab, or Herceptin) has also been approved for the treatment of breast cancer. Current research promises to produce additional agents based upon these approaches. (C) 2004 Elsevier Inc. All rights reserved.

...Abstract: cancers. The structures of the ectodomains of the ErbB receptors in their active and inactive conformation have shed light on the mechanism of receptor activation. The extracellular component of the ErbB...

...The activating growth factor, which binds to domains I and 111, selects and stabilizes a conformation that allows a dimerization arm to extend from domain II to interact with an ErbB...

...are targets for anticancer drugs. Two strategies for blocking the action of these proteins include antibodies directed against the ectodomain and drugs that inhibit protein-tyrosine kinase activity. A reversible ATP competitive inhibitor of ErbB1 (ZD1839, or Iressa) and an ErbB1 ectodomain directed antibody (IMC-C225, or Erbitux) have been approved for the treatment of non-small cell lung cancer and colorectal cancer, respectively. An ErbB2/HER2 ectodomain directed antibody (trastuzumab, or Herceptin) has also been approved for the treatment of breast cancer. Current research...
...Identifiers--EPIDERMAL-GROWTH-FACTOR; CRYSTAL-STRUCTURE; EXTRACELLULAR REGION; MONOCLONAL-ANTIBODY; CATALYTIC SUBUNIT; BREAST-CANCER; INHIBITOR; COMPLEX; ACTIVATION; DOMAINS

6/3,K,AB/5 (Item 2 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06197598 Genuine Article#: YB143 Number of References: 64
Title: Mutation of Tp53 contributes to the malignant phenotype of Abelson virus-transformed lymphoid cells (ABSTRACT AVAILABLE)
Author(s): Thome KC; Radfar A; Rosenberg N (REPRINT)
Corporate Source: TUFTS UNIV,SCH MED, DEPT PATHOL, SC315, 136 HARRISON AVE/BOSTON//MA/02111 (REPRINT); TUFTS UNIV,SCH MED, DEPT PATHOL, SC315/BOSTON//MA/02111; TUFTS UNIV,SCH MED, GRAD PROGRAM IMMUNOL/BOSTON//MA/02111; TUFTS UNIV,SCH MED, DEPT MOL BIOL & MICROBIOL/BOSTON//MA/02111
Journal: JOURNAL OF VIROLOGY, 1997, V71, N11 (NOV), P8149-8156
ISSN: 0022-538X Publication date: 19971100
Publisher: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW, WASHINGTON, DC 20005-4171
Language: English Document Type: ARTICLE
Abstract: Abelson murine leukemia virus transforms pre-B cells in vitro and induces rapid-onset pre-B-cell lymphoma in vivo. Expression of an active v-Abl protein tyrosine kinase is required for the oncogenic functions of the virus, Despite the strong growth-stimulatory signal provided by v-Abl, the virus-induced tumors are clonal or oligoclonal, and changes in the growth and oncogenic potential of in vitro transformants occur during the derivation of the cell lines. Both of these features suggest that v-Abl expression must be complemented by changes in expression of one or more cellular genes for cells to acquire a fully malignant phenotype. Such genes could include other oncogenes or tumor suppressor genes. Among the latter is Tp53, a gene mutated in many spontaneous cancers. To determine if mutation of the Tp53 tumor suppressor gene plays a role in Abelson virus transformation, conformation-specific monoclonal antibodies were used to examine p53 expression in a panel of Abelson virus-transformed pre-B cells. Expression of mutant forms of p53 was detected in over 40% of the isolates. Sequence analysis revealed the presence of point mutations affecting the highly conserved central portion of the protein. These mutations interfered with the ability of p53 to activate transcription from a promoter containing p53-responsive elements and to induce apoptosis in response to DNA damage. In addition, cells expressing mutant forms of p53 induced a higher frequency of tumors with a more rapid course compared to transformants expressing wild-type p53. These data suggest that Tp53 is one important cellular gene involved in malignant transformation by Abelson virus.

...Abstract: if mutation of the Tp53 tumor suppressor gene plays a role in Abelson virus transformation, conformation-specific monoclonal antibodies were used to examine p53 expression in a panel of Abelson virus-transformed pre-B...
...Research Fronts: FOR HETEROZYGOUS MUTATIONS)
95-4769 001 (CHRONIC MYELOGENOUS LEUKEMIA; BCR GENE; POLYMERASE CHAIN-REACTION OF BCR/ABL TRANSCRIPTS; MYELOPROLIFERATIVE DISORDERS; FLUORESCENCE IN-SITU HYBRIDIZATION)

6/3,K,AB/6 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04316197 Genuine Article#: RV120 Number of References: 34
Title: SURFACE RECRUITMENT BUT NOT ACTIVATION OF INTEGRIN ALPHA(IIB)BETA(3) (GPIIB-IIIA) REQUIRES A FUNCTIONAL ACTIN CYTOSKELETON (Abstract Available)
Author(s): ADDO JB; BRAY PF; GRIGORYEV D; FARADAY N; GOLDSCHMIDTCLERMONT PJ
Corporate Source: JOHNS HOPKINS UNIV,SCH MED,DEPT MED,DIV CARDIOL,BERNARD LAB,ROSS 1023,720 RUTLAND AVE/BALTIMORE//MD/21287; JOHNS HOPKINS

UNIV,SCH MED,DEPT MED,DIV CARDIOL,BERNARD LAB/BALTIMORE//MD/21287;
JOHNS HOPKINS UNIV,SCH MED,DEPT MED,DIV HEMATOL/BALTIMORE//MD/21287;
JOHNS HOPKINS UNIV,SCH MED,DEPT CELL BIOL & ANAT/BALTIMORE//MD/21205
Journal: ARTERIOSCLEROSIS THROMBOSIS AND VASCULAR BIOLOGY, 1995, V15, N9 (SEP), P1466-1473
ISSN: 1079-5642
Language: ENGLISH Document Type: ARTICLE
Abstract: Binding of integrin alpha(IIb)beta(3) (glycoprotein [GP] IIb-IIIa) to soluble fibrinogen requires that the receptor undergo a conformational change (receptor activation), which occurs rapidly in agonist-stimulated platelets. Agonist stimulation of platelets also results in alpha(IIb)beta(3) recruitment from intracellular membranes (alpha-granules and open canalicular system) to the platelet surface. Once activated and accessible, the receptor can engage, a process that corresponds to the binding of the receptor to its soluble fibrinogen ligand, leading to intracellular signaling reactions and centripetal migration of bound receptor molecules. Because these processes occur concurrently with a marked reorganization of the actin cytoskeleton, we investigated the role of actin in fibrinogen receptor activation and surface recruitment. We used a flow cytometric assay to directly quantitate the binding of alpha(IIb)beta(3) to fluorescently labeled fibrinogen on the platelet surface. Cytochalasin D, which inhibits elongation of actin filaments, was used to prevent the actin response to platelet agonists. Despite its ability to inhibit the actin response and alpha(IIb)beta(3) binding to the actin cytoskeleton, cytochalasin D did not alter the agonist-induced intramolecular changes resulting in increased affinity of alpha(IIb)beta(3), for soluble fibrinogen and therefore did not inhibit ADP-induced aggregation. Thus, disruption of the actin network with cytochalasin D had no effect on the dissociation constant of the complex between activated alpha(IIb)beta(3) and fibrinogen (K-d=0.26 to 0.28 mu mol/L). However, cytochalasin D suppressed the recruitment of cryptic alpha(IIb)beta(3) molecules to the platelet surface. While the physiological consequence of exposing additional alpha(IIb)beta(3) molecules on the surface of platelets is unclear, it is tempting to speculate that this process plays an important role in consolidating intra-arterial platelet thrombi, despite the shear strain generated by the arterial blood flow.

...Abstract: beta(3) (glycoprotein [GP] IIb-IIIa) to soluble fibrinogen requires that the receptor undergo a conformational change (receptor activation), which occurs rapidly in agonist-stimulated platelets. Agonist stimulation of platelets also...
...Identifiers--GLYCOPROTEIN-IIB-IIIA; PLATELET ACTIVATION; TYROSINE PHOSPHORYLATION; MONOCLONAL-ANTIBODY; CYTOCHALASIN; PROTEINS; PROFILIN; BINDING; POLYMERIZATION; REORGANIZATION
...Research Fronts: SMALL GTP-BINDING PROTEINS; CHRONIC MYELOID-LEUKEMIA; NADPH OXIDASE ACTIVATION; GDP DISSOCIATION INHIBITOR ACTIVITY; P210 BCR-ABL)
93-4323 001 (ACTIN CYTOSKELETON BEHAVIOR; GROWTH CONES; RAT MESENTERY)

6/3,K,AB/7 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04099964 Genuine Article#: RE224 Number of References: 61
Title: THE GTPASE ACTIVITY OF THE ESCHERICHIA-COLI FFH PROTEIN IS IMPORTANT FOR NORMAL GROWTH (Abstract Available)
Author(s): SAMUELSSON T; OLSSON M; WIKSTROM PM; JOHANSSON BR
Corporate Source: GOTHENBURG UNIV,DEPT BIOCHEM MED,MEDICINAREG 9/S-41390 GOTHENBURG//SWEDEN/; UMEA UNIV,DEPT MICROBIOL/S-90187 UMEA//SWEDEN/; GOTHENBURG UNIV,DEPT ANAT & CELL BIOL/S-41390 GOTHENBURG//SWEDEN/
Journal: BIOCHIMICA ET BIOPHYSICA ACTA-MOLECULAR CELL RESEARCH, 1995, V1267 , N2-3 (JUN 20), P83-91

ISSN: 0167-4889
Language: ENGLISH Document Type: ARTICLE
Abstract: The Escherichia coli (E. coli) Ffh protein is homologous to the 54kDa subunit of the eukaryotic signal recognition particle. We have examined an intrinsic GTPase activity of this protein and have created mutations in one sequence motif (GXXXXGK) of the putative GTP binding site. When glycine-112 was changed to valine (Ffh-G112V), V-max was reduced to only 4% of the wildtype level. On the other hand, when glutamine-109 was altered to glycine (Ffh-Q109G), the major effect was a 50-fold increase in K-m. These results show that the residues Q-109 and G-112 an essential for the binding and hydrolysis of GTP and that they are part of a catalytic site structurally related to that of many other GTPase proteins.

Expression of the mutant protein Ffh-G112V in E. coli was highly toxic in the presence of the wildtype protein. In contrast, genetic complementation experiments showed that a viable strain could be constructed where the Ffh-Q109G mutant protein replaced wildtype Ffh. However, expression of the mutant protein had a negative effect on growth rate at 30 degrees C and resulted in elongated cells. These results demonstrate that the GTPase activity of the Ffh protein is required for proper function of the protein in vivo.

...Identifiers--NUCLEOTIDE-BINDING DOMAIN; AMINO-ACID-SEQUENCE; H-RAS P21; 4.5S RNA; SRP-RNA; TRIPHOSPHATE ***CONFORMATION*** ; BIOCHEMICAL-PROPERTIES
...Research Fronts: SMALL GTP-BINDING PROTEINS; CHRONIC MYELOID-LEUKEMIA; NADPH OXIDASE ACTIVATION; GDP DISSOCIATION INHIBITOR ACTIVITY; P210 BCR-ABL)
93-3088 001 (RAT MUSCLE; PROTEIN PHOSPHATASE-1; MAJOR GLUTATHIONE TRANSFERASE)
93-4847 001 (HETEROLOGOUS...

...ENCODING METHYLMALONYL-COENZYME-A MUTASE)
93-6513 001 (AFFINITY PURIFICATION OF HISTIDINE-TAGGED PROTEINS; BUILDING ANTIBODIES; PLASMODIUM-FALCIPARUM ALDOLASE)

6/3,K,AB/8 (Item 5 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

02211427 Genuine Article#: KK633 Number of References: 25
Title: PHENOTYPIC AND MOLECULAR ANALYSIS OF PH1-CHROMOSOME-POSITIVE ACUTE LYMPHOBLASTIC-LEUKEMIA CELL-LINES (Abstract Available)
Author(s): MIYAGI T; OHYASHIKI J; YAMATO K; KOEFFLER HP; MIYOSHI I
Corporate Source: KOCHI MED SCH,DEPT MED/KOCHI 783//JAPAN/; TOKYO MED COLL,DEPT MED/TOKYO 160//JAPAN/; UCLA,SCH MED,CEDARS SINAI MED CTR,DEPT MED/LOS ANGELES//CA/90024
Journal: INTERNATIONAL JOURNAL OF CANCER, 1993, V53, N3 (FEB 1), P457-462
ISSN: 0020-7136
Language: ENGLISH Document Type: ARTICLE
Abstract: We have established 2 Philadelphia chromosome (Ph1)-positive acute lymphoblastic leukemia (ALL) cell lines, designated PALL-1 and PALL-2, from distinct adult Ph1-positive ALL patients. PALL-1 was established in nude mice, and PALL-2 was established in culture. Both retained the Ph1 chromosome and expressed the ALL type bcr/abl chimeric mRNA containing the junction of the first exon of BCR gene (e1) and second exon of c-abl gene (a2). PALL-1 and PALL-2 expressed CD34 surface antigen which is characteristic of early hematopoietic progenitor cells. PALL-2 expressed antigens for both pre-B and early myeloid cells and had rearrangements of both the heavy chain of immunoglobulin gene and the beta chain of T-cell-receptor gene. Both PALL-1 and PALL-2 expressed detectable levels of p53 gene

RNA. Polymerase-chain-reaction-single-strand ***conformation*** polymorphism (PCR-SSCP) analysis of the p53 gene showed a normal pattern of mobility in both cell lines. Taken together, the 2 cell lines had features of Ph1-positive ALL: (i) hematopoietic progenitor cells with pre-B-cell phenotype and, (ii) activation of e1-a2 type ***bcr*** / ***abl*** oncogene without alterations of p53 gene. These unique lines should provide a valuable tool for studying the pathogenesis of Ph1-positive ALL.

...Abstract: 2 was established in culture. Both retained the Ph1 chromosome and expressed the ALL type bcr/abl chimeric mRNA containing the junction of the first exon of BCR gene (e1) and second...

...and PALL-2 expressed detectable levels of p53 gene RNA. Polymerase-chain-reaction-single-strand conformation polymorphism (PCR-SSCP) analysis of the p53 gene showed a normal pattern of mobility in...

...hematopoietic progenitor cells with pre-B-cell phenotype and, (ii) activation of e1-a2 type bcr/abl oncogene without alterations of p53 gene. These unique lines should provide a valuable tool for...
...Research Fronts: GENE REARRANGEMENTS IN ACUTE LYMPHOBLASTIC-LEUKEMIA; MYELOID ANTIGEN EXPRESSION; DIAGNOSIS OF CELIAC-DISEASE; SERUM ANTIGLIADIN ANTIBODIES)
91-2472 001 (NUCLEOLAR ORGANIZER REGIONS; CELL CYCLE-DEPENDENT PHOSPHORYLATION OF HUMAN DNA POLYMERASE-ALPHA...
?
PLEASE ENTER A COMMAND OR BE LOGGED OFF IN 5 MINUTES

```
? ds

Set     Items   Description
S1      17747   BCR(W)ABL
S2    1678559   ANTIBOD?
S3        909   S1 AND S2
S4     533524   CONFORMATION?
S5         10   S3 AND S4
S6          8   RD  (unique items)
S7        358   S1 AND S4
S8       2734   P210
S9         45   S7 AND S8
S10        43   RD  (unique items)
S11        41   S10 AND PY<=2004
S12    584753   JUNCTION OR JOINT
S13         1   S11 AND S12
? s s7 and s12
             358  S7
          584753  S12
     S14      23  S7 AND S12
? rd
     S15      15  RD  (unique items)
? s s15 and py<=2004
Processing
              15  S15
        45236663  PY<=2004
     S16      15  S15 AND PY<=2004
? t s16/3,k,ab/1-15

 16/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2007 Dialog. All rts. reserv.
```

14947827 PMID: 15199413

Stable expression of small interfering RNA sensitizes TEL-PDGFbetaR to inhibition with imatinib or rapamycin.

Chen Jing; Wall Nathan R; Kocher Kerry; Duclos Nicole; Fabbro Doriano; Neuberg Donna; Griffin James D; Shi Yang; Gilliland D Gary

Howard Hughes Medical Institute, Division of Hematology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115, USA.

Journal of clinical investigation (United States) Jun 2004, 113 (12) p1784-91, ISSN 0021-9738--Print Journal Code: 7802877

Contract/Grant Number: CA67996; CA; NCI; DK50654; DK; NIDDK; F32 CA097802; CA; NCI; R01GM53874; GM; NIGMS

Publishing Model Print

Document type: Journal Article; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Small molecule inhibitors, such as imatinib, are effective therapies for tyrosine kinase fusions BCR-ABL-TEL-PDGFbetaR-mediated human leukemias, but resistance may develop. The unique fusion junctions of these molecules are attractive candidates for molecularly targeted therapeutic intervention using RNA interference (RNAi), which is mediated by small interfering RNA (siRNA). We developed a retroviral system for stable expression of siRNA directed to the unique fusion junction sequence of TEL-PDGFbetaR in transformed hematopoietic cells. Stable expression of the siRNA resulted in approximately 90% inhibition of TEL-PDGFbetaR expression and its downstream effectors, including PI3K and mammalian target of rapamycin (mTOR). Expression of TEL-PDGFbetaR-specific siRNA (TPsiRNA) significantly attenuated the proliferation of TEL-PDGFbetaR-transformed Ba/F3 cells or disease latency and penetrance in

mice induced by intravenous injection of these Ba/F3 cells. Although a 90% reduction in TEL-PDGFbetaR expression was insufficient to induce cell death, stable siRNA expression sensitized transformed cells to the PDGFbetaR inhibitor imatinib or to the mTOR inhibitor rapamycin. TPsiRNA also inhibited an imatinib-resistant TEL-PDGFbetaR mutant, and the inhibition was enhanced by siRNA in combination with PKC412, another PDGFbetaR inhibitor. Although siRNA delivery in vivo is a challenging problem, stable expression of siRNA, which targets oncogenic fusion genes, may potentiate the effects of conventional therapy for hematologic malignancies.

... ***2004*** ,

Small molecule inhibitors, such as imatinib, are effective therapies for tyrosine kinase fusions BCR-ABL-TEL-PDGFbetaR-mediated human leukemias, but resistance may develop. The unique fusion junctions of these ...

18575451 BIOSIS NO.: 200510269951
Molecular characterization of human CML cells with resistance to the heat shock protein (lisp) 90 inhibitor 17-allylamino-demethoxy geldanamycin (17-AAG).
AUTHOR: Bali Purva (Reprint); Fiskus Warren; Guo Fei; Annavarapu Srinivas; Sigua Celia; Sondarva Gautam; Mouttaki Abdelmoughite; Atadja Peter; Manley Paul; Bhalla Kapil N
AUTHOR ADDRESS: H Lee Moffitt Canc Ctr and Res Inst, Tampa, FL USA**USA
JOURNAL: Blood 104 (11, Part 1): p546A-547A NOV 16 2004 2004
CONFERENCE/MEETING: 46th Annual Meeting of the American-Society-of-Hematology San Diego, CA, USA December 04 -07, 2004; 20041204
SPONSOR: Amer Soc Hematol
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Poster
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Similar to AKT, c-Raf, and Src proteins, Bcr-Abl is a bonafide client protein for the chaperone, the heat shock ***protein*** (lisp) 90. Newly synthesized or stress denatured or mutant client proteins require interaction with hsp90 to maintain a mature, stable and functional ***conformation*** . Treatment with hsp90 inhibitor 17-AAG (Kosan Biosciences, Hayward, CA) disrupts the chaperone association of Bcr-Abl with hsp90, directing Bcr-***Abl*** to polyubiquitylation and proteasomaldegradation. Recently 17-AAG has been shown to have greater affinity for binding to hsp90 from cancer versus normal host cells. 17-AAG mediated down regulation of Bcr-Abl, as well as abrogation of the levels and activity of multiple pro-growth and pro-survival signaling molecules downstream of Bcr-Abl, is responsible for 17-AAG mediated differentiation and apoptosis of imatinib mesylate(IM)-sensitive and IM-refractory CML-BC cells. Indeed, 17-AAG was more activeagainst IM-refractory cells expressing mutant ***Bcr*** - ***Abl*** . In the present studieswe cultured human CML-BC K562 cells in the continuous presence of increasing levels of 17-AAG and isolated K562/AGR cells that are capable of growth in thecontinuous presence of 3.0 mu M 17-AAG. Treatment with 17-AAG (5 mu M for 24 hours) induced hsp70 levels in K562 cells. In contrast, treatment of K562/AGR cells with 5 mu M of 17-AAG, a failed to induce hsp70, and instead downregulated hsp70, hsp27 and p-HSF1 levels. While treatment with 17-AAG did not alter hsp90, it increased the levels of the co-chaperones hsp40, HOP/p60 and cdc37/p50 in K562/AGR cells. Additionally, in contrast to K562 cells, in K562/AGR cells, treatment with 17-AAG (5 mu M for 24 hours) failed to attenuate Bcr-Abl , p-AKT, p-STAT5, AKT and c-Raf levels. Although resistant to 17-AAG K562/AGR cells were as sensitive as K562 cells to apoptosis induced by the hydroxamic acid (HA) analogue histone deacetylase inhibitor (HDI)

'An activating amino acid substitution in the c-abl oncogene ***protein*** fails to produce a local ***conformational*** ***change***

Brandt-Rauf P W; Bomzer G; Belford D; Pincus M R
Department of Medicine, Columbia-Presbyterian Medical Center, New York, New York 10032.

Journal of protein chemistry (UNITED STATES) Aug 1991, 10 (4) p437-41, ISSN 0277-8033--Print Journal Code: 8217321
Contract/Grant Number: CA09529; CA; NCI; CA42500; CA; NCI
Publishing Model Print
Document type: Journal Article; Research Support, U.S. Gov't, P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

The bcr-abl chimeric gene of Philadelphia chromosome positive chronic myelogenous leukemias is only weakly transforming. This transformation activity is greatly enhanced by a Lys-for-Glu substitution at position 832 in the c-abl gene, as occurs in the highly transforming v- ***abl*** genes. It has been suggested that this mutation results in a significant structural change in the encoded ***protein*** product. Using ***conformational*** energy analysis, we have determined the allowed low-energy conformations for residues 828-836 of this ***protein*** with Lys and Glu at position 832. In both cases, the overwhelmingly preferred conformation for this region is a bend-helix motif. The helix terminates at residue 836, and there are no discernible differences in conformation between the Lys- and Glu-containing sequences. These results suggest that the activating amino acid substitution at position 832 in the c-abl protein product does not produce its effect via a local ***conformational*** ***change*** .

Solution structure of the SH2 domain of Grb2/Ash complexed with EGF receptor-derived phosphotyrosine-containing peptide.

Tsuchiya S; Ogura K; Hatanaka H; Nagata K; Terasawa H; Mandiyan V; Schlessinger J; Aimoto S; Ohta H; Inagaki F

Department of Molecular Physiology, Tokyo Metropolitan Institute of Medical Science, Bunkyo-ku, Tokyo, 113-8613, Japan.

Journal of biochemistry (JAPAN) Jun 1999, 125 (6) p1151-9, ISSN 0021-924X--Print Journal Code: 0376600

Publishing Model Print

Document type: Journal Article; Research Support, Non-U.S. Gov't

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

1H, 13C, and 15N NMR resonances of the SH2 ***domain of Grb2/Ash in both the free form and the form complexed with a phosphotyrosine-containing peptide derived from the EGF receptor were assigned by analysis of multi-dimensional, double- and triple-resonance NMR experiments. From the chemical shift changes of individual residues upon peptide binding, the binding site for the peptide was mapped on the structure of Grb2/Ash SH2. The peptide was not recognized by the groove formed by the BG and EF loops, suggesting that the EGFR peptide does not bind to Grb2/Ash SH2 in an extended ***conformation*** . This was supported by analysis of the binding affinity of mutants where residues on the BG and EF loops were ***changed*** to alanine. The present results are consistent with the recently reported structures of Grb2/Ash SH2 complexed with BCR-Abl and Shc-derived phosphotyrosine containing peptides, where the peptide forms a turn ***conformation*** . This shows that the specific conformation of the phosphotyrosine-containing sequence is required for the SH2 binding responsible for downstream signaling.

... ***1999*** ,

Inhibition of wild-type and mutant Bcr-Abl by pyrido-pyrimidine-type small molecule kinase inhibitors.

von Bubnoff Nikolas; Veach Darren R; Miller W Todd; Li Wanqing; Sanger Jana; Peschel Christian; Bornmann William G; Clarkson Bayard; Duyster Justus

Department of Internal Medicine III, Technical University of Munich, Trogerstrasse 32, D-81675 Munich, Germany.

Cancer research (United States) Oct 1 2003, 63 (19) p6395-404, ISSN 0008-5472--Print Journal Code: 2984705R

Publishing Model Print

Document type: Journal Article; Research Support, Non-U.S. Gov't

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Imatinib mesylate (STI571, Glivec), a 2-phenylaminopyrimidine small-molecule ATP competitor-type kinase inhibitor, proved to be active in Philadelphia-positive leukemias. Resistance toward imatinib develops frequently in advanced-stage Philadelphia-positive leukemia, and is even observed in chronic-phase chronic myelogenous leukemia. Point mutations within the BCR-ABL kinase domain emerged as a major mechanism of resistance toward imatinib. Mutations occur at positions that determine specific contacts of imatinib to the ATP-binding site. We aimed to examine whether pyrido-pyrimidine-type kinase inhibitors were capable of inhibiting both wild-type and mutant forms of ***BCR*** - ***ABL*** . We screened 13 different pyrido-pyrimidine with cells expressing wild-type and mutant ***BCR*** - ***ABL*** . All of the substances specifically suppressed the Bcr-Abl dependent phenotype and inhibited Bcr-***Abl*** kinase activity with higher potency than imatinib. Two of the most active compounds were PD166326 and SKI DV-M016. Interestingly, these compounds suppressed the activation loop mutant Bcr-Abl H396P as effectively as wild-type ***Bcr*** - ***Abl*** . In addition, nucleotide-binding loop mutations (Y253H, E255K, and E255V) were selectively and potently inhibited. In contrast, T315I, a mutant located at a position that makes a direct contact with imatinib, was not affected. This observation is consistent with the hypothesis that unlike imatinib, pyrido-pyrimidine inhibitors bind Bcr-Abl regardless of the ***conformation*** of the activation loop. We conclude that pyrido-pyrimidine-type kinase inhibitors are active against differen

Mechanisms and implications of imatinib resistance mutations in BCR - ***ABL***

Nardi Valentina; Azam Mohammad; Daley George Q
Whitehead Institute, 9 Cambridge Center, Cambridge, MA 02142, USA.

Current opinion in hematology (United States) Jan 2004, 11 (1) p35-43, ISSN 1065-6251--Print Journal Code: 9430802
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

PURPOSE OF REVIEW: Aside from bone marrow transplantation, a definitive cure for Philadelphia (Ph) chromosome-positive chronic myeloid leukemia (CML) has yet to be developed. Although Imatinib, the first molecularly targeted drug developed for CML has achieved a remarkable success, the emergence of resistance to this agent mitigates the prospect of a cure for this leukemia. Though a variety of resistance mechanisms can arise, in the majority of patients resistance coincides with reactivation of the tyrosine kinase activity of the ***BCR*** - ***ABL*** fusion oncoprotein. This can result from gene amplification and, more importantly, point mutations that disrupt the bind of imatinib to ***BCR*** - ***ABL*** itself. In this review, we aim to define and illuminate mechanisms of resistance and describe how drug resistance is shedding new light on kinase domain regulation. RECENT FINDINGS: In light of recent studies and publications, it is now clear that Imatinib exerts its inhibitory action by stabilizing the inactive non ATP-binding conformation of BCR-ABL and that mutations even outside the kinase domain can lead to enhanced autophosphorylation of the kinase, thereby stabilizing the active conformation that resists imatinib binding. So far, 25 ***different*** substitutions of 21 amino acid residues of ***BCR*** - ***ABL*** have been detected in CML patients. In addition, it has been recently illustrated that mutations preexist the onset of treatment and that some confer a more aggressive disease phenotype. Finally it has been shown that molecular remission is almost never reached through Imatinib therapy. SUMMARY: The most common mechanism of relapse for CML patients treated with Imatinib is the appearance of point mutations in the BCR-ABL oncogene that confer resistance to this drug. Insights into the emerging problem of resistance

Regulation of the c- ***Abl*** and ***Bcr*** - ***Abl*** tyrosine kinases.

Hantschel Oliver; Superti-Furga Giulio
Developmental Biology Programme, European Molecular Biology Laboratory, Meyerhofstrasse 1, 69117 Heidelberg, Germany. hantschel@embl-heidelberg.de

Nature reviews. Molecular cell biology (England) Jan ***2004*** , 5 (1) p33-44, ISSN 1471-0072--Print Journal Code: 100962782
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

The prototypic non-receptor tyrosine kinase c-Abl is implicated in various cellular processes. Its oncogenic counterpart, the ***Bcr*** - ***Abl*** fusion ***protein*** , causes certain human leukaemias. Recent insights into the structure and regulation of the c-Abl and Bcr -Abl tyrosine kinases have changed the way we look at these enzymes.

Pyrido-pyrimidine kinase inhibitors suppress wild-type and mutant Bcr-Abl.

AUTHOR: von Bubnoff Nikolas (Reprint); Veach Darren R; Miller W Todd; Li Wanqing; Saenger Jana (Reprint); Peschel Christian (Reprint); Bornmann William G; Clarkson Bayard; Duyster Justus (Reprint)
AUTHOR ADDRESS: Department of Internal Medicine III, Technical University of Munich, Munich, Germany**Germany
JOURNAL: Blood 102 (11): p230a November 16, 2003 2003
MEDIUM: print
CONFERENCE/MEETING: 45th Annual Meeting of the American Society of Hematology San Diego, CA, USA December 06-09, 2003; 20031206
SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Imatinib mesylate (STI571, Gleevec), a 2-phenylaminopyrimidine ATP competitor-type kinase inhibitor, proved to be active in Philadelphia-positive (Ph+) leukemias. Resistance towards imatinib frequently develops in advanced-stage Ph+ leukemia, and is even observed in chronic phase chronic myelogenous leukemia (CML). The major mechanism of resistance towards imatinib turned out to be point mutations within the BCR-ABL kinase domain. Mutations occur at positions that determine specific contacts of imatinib to the ATP-binding site. Pyrido-pyrimidines constitute a class of small-molecule kinase inhibitors that exhibit a mode of binding to the ATP-binding site of Bcr-Abl that is distinct from imatinib. Therefore, we aimed to examine if pyrido-pyrimidine-type kinase inhibitors were capable of inhibiting both wild-type, and clinically relevant mutant forms of BCR-ABL. We examined thirteen different pyrido-pyrimidines using cells expressing wild-type and mutant BCR-ABL. All substances specifically suppressed the Ber-Abl dependent phenotype and inhibited Ber-Abl kinase activity with higher potency compared to imatinib. Growth suppression of Bcr-Abl transformed cells was accompanied by inhibition of Bcr-Abl Kinase activity, inhibition of Stat5 activation, and induction of apoptosis. The most active compounds were SKI DV 2-43, PD166326 and SKIDV-MO16. Differential activities towards different mutant forms of Bcr-Abl were as follows: The activation loop mutant Bcr-Abl H396P was suppressed as effectively as wild-type Bcr-Abl by all pyrido-pyrimidines that were analyzed. This observation is consistent with the hypothesis that unlike imatinib, pyrido-pyrimidine inhibitors bind Bcr-Abl regardless of the ***conformation*** of the activation loop. The nucleotide-binding (P) loop comprises the most frequently occuring mutations in cases of imatinib resistant Ph+leukemia with Y253 and E255 being affected in the majority of cases. As opposed to imatinib, pyrido-pyrimidines demonstrated to be selective and potent inhibitiors of Bcr-Abl Y253H, E255K and E255V. In contrast, pyrido-pyrimidines did not suppress Bcr-Abl T315I, a mutant located at a position that makes a direct contact with imatinib. An exchange from threonine to isoleucine adds an extra hydrocarbon group in the amino acid side chain that presumably causes a steric clash with both type of compounds. We conclude, that pyrido-pyrimidine-type kinase inhibitors are more potent inhibitors of ***wild*** - ***type*** Ber-Abl than imatinib. This could be favourable in terms of rapidly eradicating the Ph+ disease, thereby hindering clones with Bcr-Abl amplification to come up that maintain a baseline level of signaling that would be sufficient for cell survival in the presence of imatinib. Moreover, pyrido-pyrimidines are active in frequently detected mutant forms of Bcr-Abl that cause resistance towards imatinib. Pyrido-pyrimidines may therefore be used not only to treat imatinib-resistant disease, but as well to prevent resistant disease clones to emerge.

Pyrido-pyrimidine kinase inhibitors suppress wild-type and

mutant Bcr-Abl.
2003

...ABSTRACT: we aimed to examine if pyrido-pyrimidine-type kinase inhibitors were capable of inhibiting both wild-type, and clinically relevant mutant forms of BCR-ABL. We examined thirteen different pyrido-pyrimidines using cells expressing wild-type and mutant BCR-ABL. All substances specifically suppressed the Ber-Abl dependent phenotype and inhibited...

...were as follows: The activation loop mutant Bcr-Abl H396P was suppressed

```
      ---  -----  -----------
? s (bcr(w)abl) 10n (conformation?)
>>>Invalid syntax
? s (bcr(w)abl) (10n) (conformation?)
           27076  BCR
           26734  ABL
          533931  CONFORMATION?
      S1      81  (BCR(W)ABL) (10N) (CONFORMATION?)
? rd
      S2      46  RD  (unique items)
? s wild(w)type
          500586  WILD
         2995178  TYPE
      S3  388420  WILD(W)TYPE
? s s2 and s3
              46  S2
          388420  S3
      S4      10  S2 AND S3
? s s4 and py<=2004
Processing
              10  S4
        45236698  PY<=2004
      S5       3  S4 AND PY<=2004
? t s5/3,k,ab/1-3

 5/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
```